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July 20, 2005

Mr. Stephen Johnson, Administrator
U.S. Environmental Protection Agency
Ariel Rios Building, 1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on the HPV Test Plan for Tetrabutylhexamethylenediamine

Dear Administrator Johnson:

The following comments on Solutia's test plan for the chemical tetrabutylhexamethylenediamine are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

Solutia submitted their test plan on March 18, 2005, for the chemical tetrabutylhexamethylenediamine (CAS No. 27090-63-7), referred to as TBHMD. This chemical is used as an intermediate in the manufacture of 1,6-bis(dibutylethylammonium), or BQAOH. BQAOH is then used in the production of nylon-6,6. There is limited toxicity information on TBHMD and Solutia proposes to conduct a number of studies to fill data gaps including an acute fish test (OECD 203) and a combined reproductive and developmental toxicity test (OECD 421). If conducted, these tests will result in the death of 40-120 fish and 675 mammals.

Acute fish tests with this chemical are unnecessary as the log $K_{o/w}$ of TBHMD is 4.56 to 7.59 (test plan, p. 8), and the EPA has stated that acute fish tests are inappropriate for compounds with log $K_{o/w}$ values above 4.2 (EPA, 2000). Furthermore, Solutia plans to carry out an acute fish toxicity study on BQAOH, which is also sponsored in the HPV program. These data could be used in a "read-across" approach to fill the SIDS endpoint for acute fish toxicity with TBHMD and no additional testing should be conducted. This is a scientifically valid approach as the toxicity of TBHMD and BQAOH are similar in that both are mediated by their activity at the nicotinic receptor. Although the toxicity of bis tertiary amines such as TBHMD is less potent than that of bis quaternary amines such as BQAOH, hazard data for the more potent compound is sufficient to meet the acute fish toxicity endpoint in a screening level program such as HPV.

We also disagree with Solutia's proposal to conduct a combined reproductive/developmental screen with TBHMD. Although no data were located on the reproductive and developmental hazards of this chemical *per se*, we do not believe additional testing is warranted simply to "check-the-box" for these SIDS endpoints. Histopathological evaluation from the 90-day repeated dose study did not reveal any toxic effects of TBHMD in the reproductive organs of

rats. Moreover, it is unlikely that the test material will cross the placenta in concentrations that will selectively affect the fetus due to its physicochemical properties: it is charged at physiologic pH and probably highly protein bound (test plan, p. 14). In addition, developmental studies on a structurally similar chemical, hexamethylene diamine (HMD), were negative; although one study reported a fetal NOAEL lower than that of the maternal animal (Kennedy, 2005). Although Solutia does not consider HMD to be a close enough analog to TBHMD, we submit, in this instance, that the totality of information on this class of chemicals could be used in a weight-of-evidence approach with no additional testing conducted with TBHMD. Bi-tertiary amines such as TBHMD, have been shown to act as blockers at nicotinic ganglia and neuromuscular junctions in mammals (test plan, p. 10). As a class, nicotinic ganglionic blockers have been studied since the earliest days of pharmacology research. Information from this class of chemicals, in particular, competitive binding to ganglionic cholinoceptive sites and prevention of post-synaptic depolarization (prototype hexamethonium), can be used to inform the toxicity of TBHMD. Taken together, these data provide sufficient hazard information to assess the potential toxicity of TBHMD without conducting additional animal studies.

If Solutia wishes to investigate the developmental toxicity of TBHMD, we ask that they first further evaluate whether metabolites would cross the placenta before initiating testing.

Thank you for your attention to these comments. I may be reached at 202-686-2210, ext. 327, or via e-mail at meven@pcrm.org.

Sincerely,

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References

EPA. Data collection and development on high production volume (HPV) chemicals. *Federal Register* 2000; 65(248).

Kennedy GL. Toxicity of hexamethylenediamine. *Drug Chem Toxicol* 2005; 28: 15-33.

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TBHMD Test Plan.pdf


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